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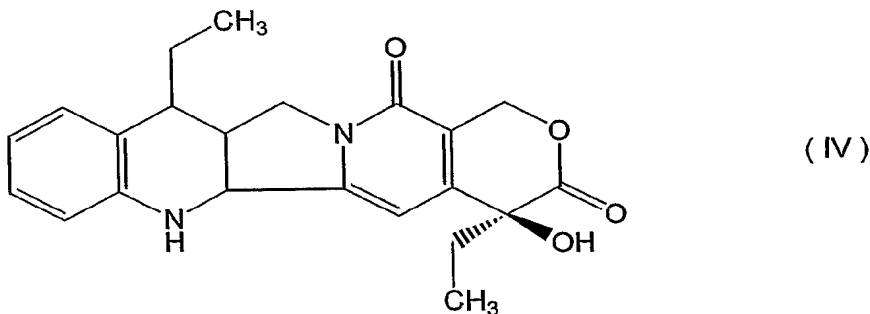
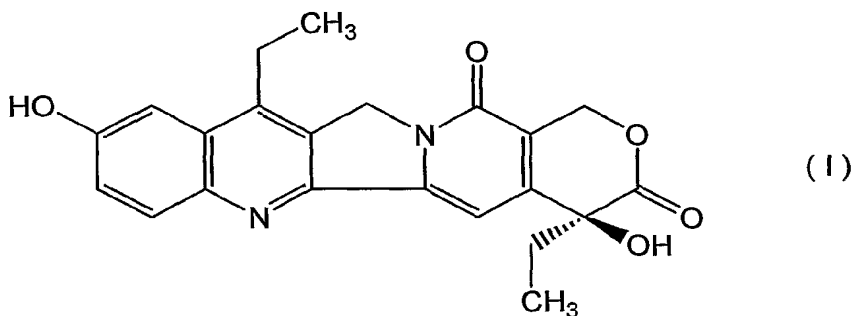
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[Continued on next page]

(54) Title: THE METHOD OF MANUFACTURING OF 7-ETHYL-10-HYDROXYCAMPTOTHECIN



(57) Abstract: The method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV is oxidized with an oxidizing agent selected from the group comprising iodosobenzene, an ester of iodosobenzene, sodium periodate, potassium periodate, potassium peroxodisulfate and ammonium peroxodisulfate, in a solvent formed by a saturated aliphatic monocarboxylic acid containing 1 to 3 carbon atoms, and in the presence of water.

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**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,

HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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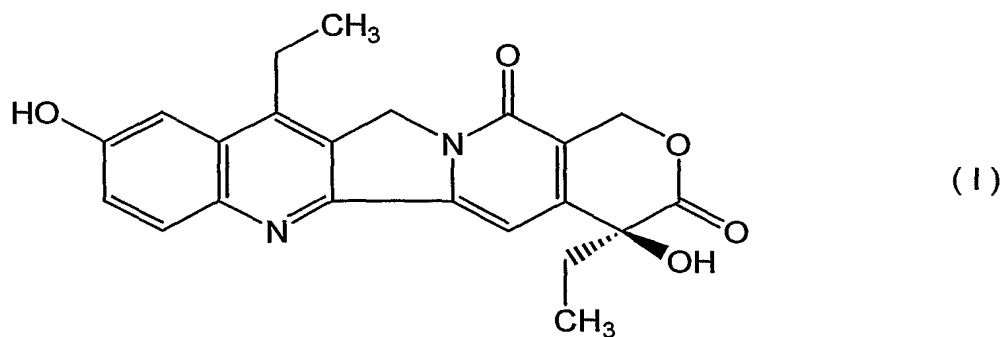
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## The Method of Manufacturing of 7-Ethyl-10-hydroxycamptothecin

### Field of the Invention

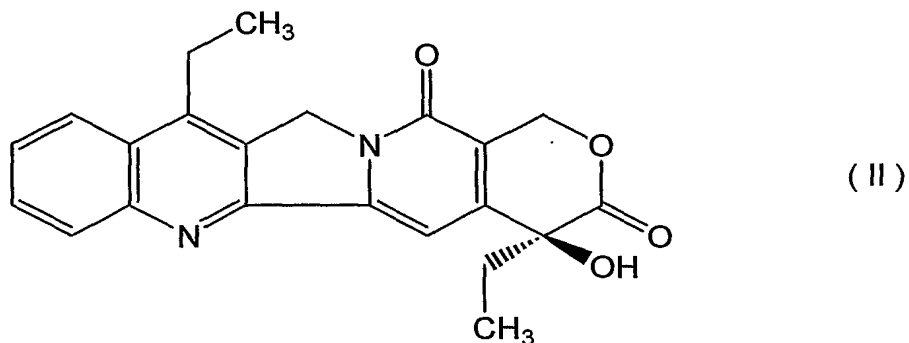
This invention relates to the method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I



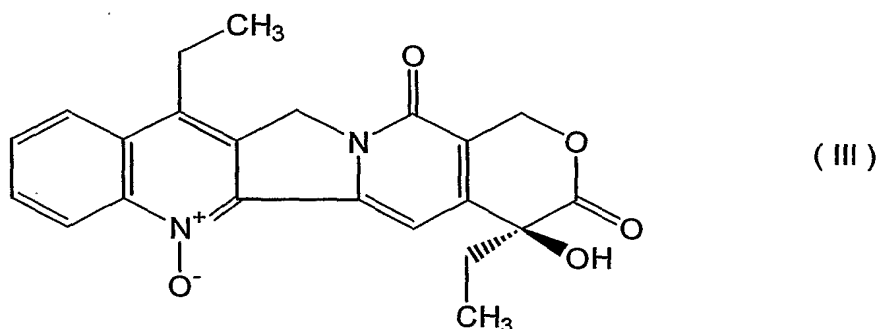
which is used for manufacturing of cytostatically active irinotecan hydrochloride trihydrate, effective particularly in treatment of lung and rectum cancer. The cytostatic effect of irinotecan hydrochloride trihydrate is based on its ability to inhibit topoisomerase.

### Background of the Invention

So far, 7-ethyl-10-hydroxycamptothecin is usually prepared in two reaction steps. In the first reaction step, 7-ethylcamptothecin of formula II



is oxidized with hydrogen peroxide in acetic acid under formation of 7-ethylcamptothecin 1-oxide of formula III



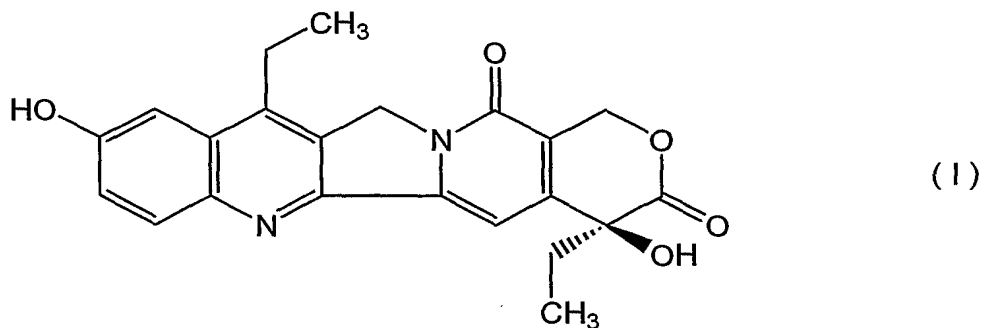
which in the second reaction step is dissolved in the solvent system dioxane-acetonitrile-water and the solution is irradiated with UV light in the presence of sulfuric acid to afford the desired 7-ethyl-10-hydroxycamptothecin (see US 4 473 692 and US 4 513 138 and Zhongguo Yaowu Huaxue Zazhi 2001, 11 (4), 238-240).

However, this method of manufacturing of 7-ethyl-10-hydroxycamptothecin suffers from the fact that the oxidation of 7-ethylcamptothecin in the first reaction step requires relatively great amount of acetic acid (300 ml of acetic acid per 1 gram of 7-ethylcamptothecin). In the isolation of the obtained 7-ethylcamptothecin 1-oxide it is necessary to evaporate one fourth of the acetic acid volume, add water to the evaporation residue and subsequently collect the precipitated 7-ethylcamptothecin 1-oxide by filtration. This isolation procedure is demanding and affects very unfavourably the yield of 7-ethylcamptothecin 1-oxide. In the second step, the isolation of 7-ethyl-10-hydroxycamptothecin, consists in removal of the solvent mixture by distillation, dilution with water, extraction with chloroform and drying the chloroform layer over magnesium sulfate, followed by purification on a silica gel column with the aim to remove impurities arising in the UV irradiation. In spite of this complicated isolation procedure, the obtained 7-ethyl-10-hydroxycamptothecin still contains up to 22 % by weight of 7-ethylcamptothecin. In this method the total yield of both reaction steps is only about 38 %.

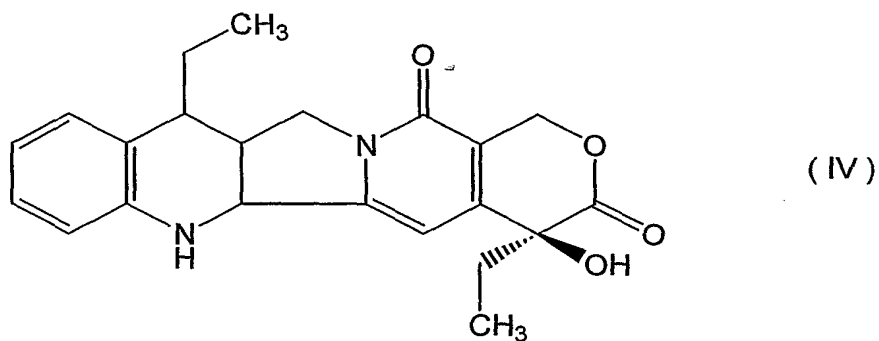
The aim of the invention is to find a less demanding method of producing 7-ethyl-10-hydroxycamptothecin that would afford 7-ethyl-10-hydroxycamptothecin in higher yields and higher purity. This aim has been achieved by the method according to the present invention.

### Summary of the Invention

The present invention relates to the method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I

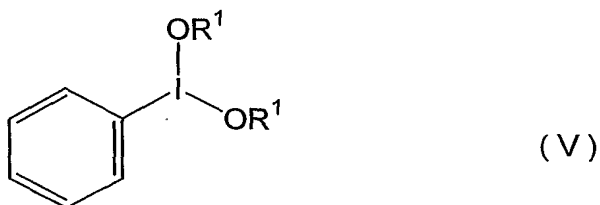


which is characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV



is oxidized with an oxidizing agent selected from the group comprising iodosobenzene, an ester of iodosobenzene, sodium periodate, potassium periodate, potassium peroxodisulfate and ammonium peroxodisulfate, in the presence of a solvent formed by a saturated aliphatic monocarboxylic acid comprising 1 to 3 carbon atoms, and in the presence of water.

The oxidizing agent is preferably an ester of iodosobenzene, more preferably an ester of iodosobenzene of general formula V



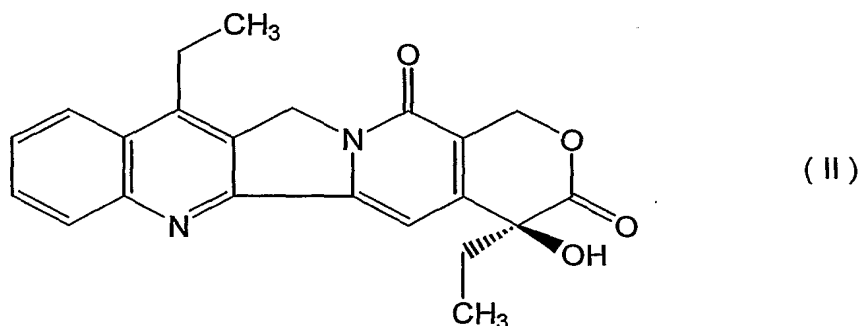
in which substituents  $R^1$  are the same or different and designate hydrogen,  $-C(O)-R^2$  or  $-SO_2-R^3$  where  $R^2$  and  $R^3$  independently are selected from a group comprising an optionally substituted alkyl group having 1 to 6 carbon atoms, an optionally substituted cycloalkyl group having 3 to 8 carbon atoms, an optionally substituted aryl group having 6 to 12 carbon atoms, and an optionally substituted aralkyl group in which the aryl moiety has 6 to 12 carbon atoms and the alkyl moiety has 1 to 4 carbon atoms, with the proviso that at least one of the substituents  $R^1$  is not the hydrogen atom, in particular an ester of iodobenzene selected from a group comprising iodobenzene diacetate, iodobenzene bis(trifluoroacetate) and hydroxy(tosyloxy)iodobenzene. Iodobenzene diacetate is advantageously used in an amount of 0.99 to 1.85 mol, more advantageously 1.28 to 1.56 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

Suitable solvents include acetic acid, formic acid or trifluoroacetic acid. Preference is given to acetic acid in amounts from 668 to 1001 mol, more preferably 751 to 918 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

Water is advantageously used in amounts from 0.98 to 1.88 mol, preferably from 1.28 to 1.58 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

The oxidation is carried out preferably at a temperature in the range of 15 to 30 °C, more preferably at 18 to 25 °C, the reaction time being 5 to 30 minutes, more preferably 10 to 15 minutes.

The starting 7-ethyl-1,2,6,7-tetrahydrocamptothecin is preferably obtained by hydrogenation of 7-ethylcamptothecin of formula II



in a saturated aliphatic monocarboxylic acid having 1 to 3 carbon atoms, using hydrogen in the presence of a hydrogenation catalyst and a sulfur compound partly deactivating the hydrogenation catalyst.

Preferred saturated aliphatic monocarboxylic acids are formic acid, acetic acid or trifluoroacetic acid, more preferred being acetic acid in an amount of 791 to 1187 mol, most preferably 890 to 1088 mol, per 1 mol of 1-ethylcamptothecin.

Preferred sulfur compound that partly deactivates the hydrogenation catalyst is dimethyl sulfoxide, preferably in an amount of 0.18 to 0.33 mol, more preferably in an amount of 0.23 to 0.28 mol, per 1 mol of 7-ethylcamptothecin.

Preferred hydrogenation catalyst is a noble metal, preferably platinum which is advantageously used on a carrier consisting of an activated carbon or aluminum oxide. Platinum is advantageously used in an amount of 0.018 to 0.027 mol, more advantageously in an amount of 0.020 to 0.025 mol, per 1 mol of 7-ethylcamptothecin, in the form of hydrogenation catalyst consisting of platinum on an activated carbon with platinum content of 5 %. The hydrogenation is performed advantageously at a pressure from 0.3 to 0.7 MPa, more preferably at 0.4 to 0.6 MPa, at a temperature from 45 to 85 °C, more preferably at 58 to 72 °C, for 24 to 70 hours, more preferably for 40 to 50 hours.

After the end of the oxidation, undesired compounds are removed in the following way. The solvent is distilled off, 7-ethyl-10-hydroxycamptothecin is precipitated in acetonitrile and isolated by filtration and washing with acetonitrile. In the procedure according to the present invention, at least 58 % yield of 7-ethyl-10-hydroxycamptothecin is achieved in a relative purity of 90 %, as determined by high performance liquid chromatography.

A substantial advantage of the method according to this invention over the prior art ones is that in the oxidation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin no coloured side products are formed that need be removed by chromatography on a silica gel column. In an advantageous embodiment of this invention, the oxidation is preceded by hydrogenation of 7-ethylcamptothecin under formation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin which advantageously is not isolated, the oxidation being performed directly with the obtained hydrogenation mixture from which only the hydrogenation catalyst has been removed.

In the following example, the method according to this invention is described in more detail, this example being for illustration only, without limiting in any way the scope of the invention which is unequivocally defined by the patent claims and the description part.

## Examples

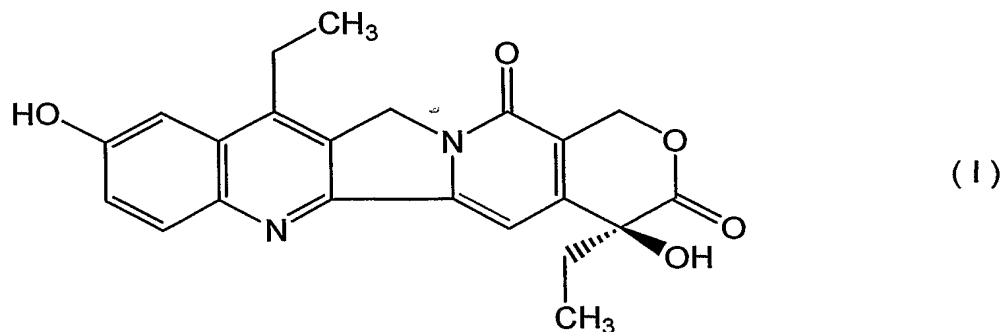
### Example 1

In a 100 ml beaker, 0.5 g (1.239 mmol) of 7-ethylcamptothecin, 0.32 g of 5% hydrogenation catalyst Pt/C (containing 0.028 mmol of platinum) and 0.025 ml (0.352 mmol) of dimethyl sulfoxide are added to 70 ml of acetic acid. The obtained suspension is quantitatively transferred into a 100 ml autoclave. After closure, the autoclave is flushed three times with nitrogen at the pressure of 0.5 MPa and then three times with hydrogen at the pressure of 0.5 MPa. The temperature is adjusted to 65 °C and the mixture is stirred at 950 r.p.m. The hydrogen pressure is adjusted to 0.5 MPa. After 43.5 hours the consumption of hydrogen stops and the procedure is terminated. After cooling to 25 °C, the stirring is stopped and the internal pressure is equilibrated with the ambient atmosphere. The autoclave is flushed three times with nitrogen, the hydrogenation catalyst is removed from the hydrogenation mixture by filtration under pressure of nitrogen and the catalyst cake is washed with 10 ml of acetic acid. The obtained solution (80 ml) of 7-ethyl-1,2,6,7-tetrahydrocamptothecin is immediately added under vigorous stirring into a 250 ml one-necked flask containing 22 ml (1.218 mol) of water and 0.77 g (2.343 mmol) of iodobenzene diacetate. The obtained solution is stirred for 15 minutes at 22 °C. Then the solvent is evaporated and the residue is mixed with 10 ml of acetonitrile. The obtained suspension is homogenized by sonication. The solid 7-ethyl-10-hydroxycamptothecin is isolated by filtration, washed on the filter with 10 ml of acetonitrile and dried to the constant weight in a vacuum oven at 60 °C to 65 °C. The yield of 7-ethyl-10-hydroxycamptothecin is 0.283 g (58.3 %). Its relative purity, determined by high performance liquid chromatography, is 90.2 %.

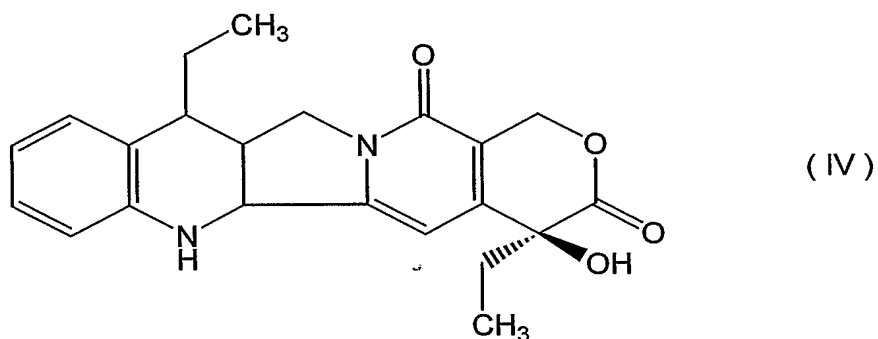


## CLAIMS

1. The method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I



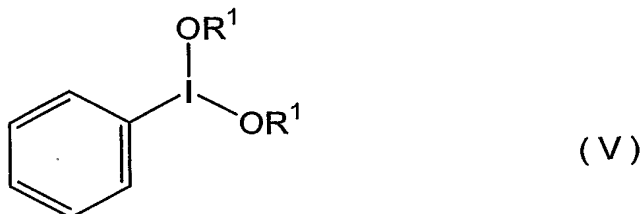
characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV



is oxidized with an oxidizing agent selected from the group comprising iodosobenzene, an ester of iodosobenzene, sodium periodate, potassium periodate, potassium peroxodisulfate and ammonium peroxodisulfate, in a solvent formed by a saturated aliphatic monocarboxylic acid containing 1 to 3 carbon atoms, and in the presence of water.

2. The method according to claim 1, characterized in that the oxidizing agent is an ester of iodosobenzene.

3. The method according to claim 2, characterized in that the ester of iodobenzene is an ester of iodobenzene of general formula V



wherein substituents  $R^1$  are the same or different and designate hydrogen,  $-C(O)-R^2$  or  $-SO_2-R^3$  where  $R^2$  and  $R^3$  independently are selected from a group comprising an optionally substituted alkyl group having 1 to 6 carbon atoms, an optionally substituted cycloalkyl group having 3 to 8 carbon atoms, an optionally substituted aryl group having 6 to 12 carbon atoms, and an optionally substituted aralkyl group wherein the aryl moiety has 6 to 12 carbon atoms and the alkyl moiety has 1 to 4 carbon atoms, with the proviso that at least one of the substituents  $R^1$  is not the hydrogen atom.

4. The method according to claims 1 to 3, characterized in that the oxidizing agent is an ester of iodobenzene selected from the group comprising iodobenzene diacetate, iodobenzene bis(trifluoroacetate) and hydroxy(tosyloxy)iodobenzene.

5. The method according to claims 1 to 4, characterized in that the oxidizing reagent is iodobenzene diacetate in an amount of 0.99 to 1.85 mol, preferably 1.28 to 1.56 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

6. The method according to claim 1, characterized in that the solvent is acetic acid, formic acid or trifluoroacetic acid.

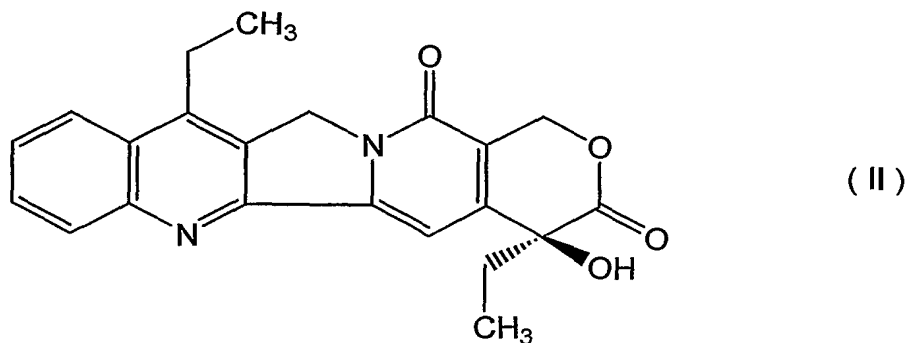
7. The method according to claim 6, characterized in that the solvent is acetic acid in an amount of 668 to 1001 mol, preferably 751 to 918 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

8. The method according to claims 1 to 7, characterized in that water is used in an amount of 0.98 to 1.88 mol, preferably 1.28 to 1.58 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

9. The method according to claim 1, characterized in that the oxidation is carried out at a temperature from 15 to 30 °C, preferably at 18 to 25 °C.

10. The method according to claim 1, characterized in that the oxidation is performed for 5 to 30 minutes, preferably for 10 to 15 minutes.

11. The method according to claim 1, characterized in that the starting 7-ethyl-1,2,6,7-tetrahydrocamptothecin is obtained by hydrogenation of 7-ethylcamptothecin of formula II



in a saturated aliphatic monocarboxylic acid having 1 to 3 carbon atoms, using hydrogen in the presence of a hydrogenation catalyst and a sulfur compound that partly deactivates the hydrogenation catalyst.

12. The method according to claim 11, characterized in that the saturated aliphatic monocarboxylic acid is formic acid, acetic acid or trifluoroacetic acid.

13. The method according to claim 12, characterized in that acetic acid is used in an amount of 791 to 1187 mol, preferably 890 to 1088 mol, per 1 mol of 7-ethylcamptothecin.

14. The method according to claim 11, characterized in that the sulfur compound that partly deactivates the hydrogenation catalyst is dimethyl sulfoxide.

15. The method according to claim 14, characterized in that dimethyl sulfoxide is used in an amount of 0.18 to 0.33 mol, preferably 0.23 to 0.28 mol, per 1 mol of 7-ethylcamptothecin.

16. The method according to claim 11, characterized in that the hydrogenation catalyst is a noble metal.

17. The method according to claim 16, characterized in that the noble metal is platinum.

18. The method according to claim 17, characterized in that platinum is used on an activated carbon or aluminum oxide carrier.

19. The method according to claim 18, characterized in that platinum is used in an amount of 0.018 to 0.027 mol, preferably 0.020 to 0.025 mol, per 1 mol of 7-ethylcamptothecin, in the form of a hydrogenation catalyst, formed by platinum on an activated carbon with platinum content 5 %.

20. The method according to claim 11, characterized in that the hydrogenation is carried out at a pressure from 0.3 to 0.7 MPa, preferably at a pressure from 0.4 to 0.6 MPa.

21. The method according to claim 11, characterized in that the hydrogenation is carried out at a temperature from 45 to 85 °C, preferably at 58 to 72 °C.

22. The method according to claim 11, characterized in that the hydrogenation is carried out for 24 to 70 hours, preferably for 40 to 50 hours.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CZ2004/000085

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/22  
 //(C07D491/22, 311:00, 221:00, 221:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WOOD J L ET AL: "An Efficient Conversion of Camtothecin to 10-Hydroxycamptothecin" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 60, 1995, pages 5739-5740, XP002323603 ISSN: 0022-3263 page 5739, right-hand column, paragraph 1 - page 5740, left-hand column, last paragraph; examples; compounds 4,2	1-22
Y	US 4 473 692 A (MIYASAKA ET AL) 25 September 1984 (1984-09-25) column 7, line 11 - line 62; claim 37; example 7 column 9, line 28 - line 64 ----- -/--	1-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

7 April 2005

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 734 056 A (BURK ET AL) 31 March 1998 (1998-03-31) column 4, line 33 - column 5, line 67; claim 1; example 6 column 10, line 34 - column 12, line 46 -----	1-22
P,X	W0 2004/100897 A (SCINOPHARM TAIWAN, LTD) 25 November 2004 (2004-11-25) page 3 - page 5; claim 2 page 6, line 3 - page 7, line 17 page 4, line 25 - line 28 -----	1-22

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Information on patent family members

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